AMENDMENTS TO THE DRAWINGS

Please replace the drawings with the replacement drawings labeled as "Replacement Sheet".

REMARKS/ARGUMENTS

Reconsideration of the present application, as amended, is respectfully requested.

A. CLAIM AMENDMENTS

As a result of the present amendment, claims 1, 5, 8, 11-18 are presented in the case for continued prosecution.

The subject matter of cancelled claims 2, 3 (only βig-h3), 4 and 6 has been added to claim 1. Applicants have noted a typographical error concerning the concentration range of βig-h3 in claim 6 and the specification, and amended the erroneous range, "100 μg/ml ~ 1 μg/ml", to "100 μg/ml ~ 1 **mg**/ml". The typographical error is apparent as shown from the preferred range, "300 μg/ml ~ 600 μg/ml" and the more preferred concentration, "450 μg/ml". Support can be found, for example, at page 18, lines 5-6 and Example 2 at page 23.

Claims 5 and 8 are amended to change dependency. Claims 7 and 9-10 are cancelled without prejudice. New claims 11-18 have been added. Support for claim 11 can be found, for example, in Example 2 at page 23. Support for claims 12-15 can be found, for example, in Examples 1 and 2 at page 23. Support for claims 16-18 can be found, for example, at page 17, lines 8-15 and page 18, lines 10-13. No new matter has been added.

B. DRAWINGS

The drawings were objected to by the Examiner. In response thereto, Applicants have submitted replacement drawing sheets. It is urged that the replacements are in proper form. The Examiner has not provided any comment concerning the informalities or provided a PTO-948 form indicating the corrections required. In the event that the Examiner continues to object to the drawings, Applicants respectfully request clarification.

C. THE CLAIMED INVENTION

The present invention is directed to compositions for stimulating bone-formation and bone-consolidation. The compositions include water-soluble chitosan and tripolyphospate in which the water-soluble chitosan contains βig-h3 at a concentration of 100 μg/ml ~ 1 mg/ml. The mixed ratio of the water-soluble chitosan and the tripolyphospate is in a range of 20:80 ~ 80:20 weight %. The βig-h3 stimulates bone-formation and bone-consolidation and therefore

enhances the efficacy of the water-soluble chitosan and the tripolyphosphate. Thus, the compositions of the present invention allow advantageously a shortened bone-generation period.

D. CLAIM REJECTIONS UNDER 35 U.S.C. §102(b)

1. The Claimed Invention is Not Anticipated by Hansson

At pages 2-3 of the Office Action, the Examiner has rejected the subject matter of original claims 1-3 under 35 USC 102(b) as allegedly anticipated by Hansson et al. (WO 96/02259).

Hansson et al. relates to uses of chitosan and polysaccharide such as heparin and chondroitinsulphates, for stimulating regeneration of hard tissue. Hansson et al. discloses adding an aqueous solution 2% w/v chitosan to a solution of dextransulphate or heparin or chondroitin-4-sulphate (0.1% w/v) in tripolyphosphate buffer.

Applicants call attention to the requirement that a rejection under 35 U.S.C. 102(b) requires that all of the elements of the rejected claims be found within the cited reference.

Hansson et al. does **not**, however, disclose βig-h3 at a concentration of 100 μg/ml ~ 1 mg/ml. On the contrary, the compositions of the claimed invention include the water-soluble chitosan containing the βig-h3 protein at a concentration of 100 μg/ml ~ 1 mg/ml and the tripolyphosphate. The results of the measurements of bone mineral density and newly-formed bone volume show that adding the βig-h3 protein stimulates bone-formation and bone-consolidation. See page 28, lines 19-23; last paragraph bridging pages 31 and 32; Figures 8A and 8B; and Figures 11B and 11C ("βig-h3 group" represents compositions including the water-soluble chitosan containing βig-h3 and the tripolyphosphate whereas "chitosan group" represents compositions including the water-soluble chitosan and the tripolyphosphate).

Additionally, Hansson et al. does **not** teach the mixed ratio of the tripolyphosphate to the water-soluble chitosan being in a range of 20:80 ~ 80:20 weight %.

Thus, it is respectfully urged that the claimed invention is not anticipated by Hansson et al. Reconsideration and removal of the rejection is respectfully requested.

2. The Claimed Invention is Not Anticipated by Shu

Original claims 1, 2 and 4 are also rejected under 35 USC 102(b) as allegedly anticipated by Shu et al. (International Journal of Pharmaceutics 2000, 201, 51-58). Shu et al. relates to

tripolyphosphate/chitosan complex beads for sustained drug release. Shu et al. discloses a composition of 4% chitosan and 1% tripolyphosphate.

The Examiner is reminded that a rejection under 35 U.S.C. 102(b) requires that all of the elements of the rejected claims be found within the cited reference.

Shu et al. does not disclose adding the βig-h3 to the water-soluble chitosan, let alone at a concentration of 100 μg/ml ~ 1 mg/ml as required by the compositions of claim 1. The βig-h3 stimulated bone-formation and bone-consolidation.

Accordingly, the composition of claim 1 is distinguishable over that of Shu et al. Thus, it is respectfully urged that the claimed invention is not anticipated by Shu et al. Reconsideration and removal of this rejection is respectfully requested.

E. CLAIM REJECTIONS UNDER 35 U.S.C. §103(a)

1. Summary of the Rejections

At pages 4-8 of the Office Action, the Examiner has rejected the subject matter of pending claims under 35 U.S.C. 103(a) as allegedly unpatentable over Hansson et al. in view of Kim et al. (Journal of Cellular Biochemistry, 2000, 77, 169-178) and Shu et al. and Santos et al. (US Patent No. 5,955,096) and Wilson et al. (Development 1997, 124, 3177-3184).

The Examiner has alleged that it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the composition of Hansson et al. with a material for stimulating bone-formation and bone-consolidation selected from a group consisting of βig-h3, bone morphogenic protein, TGF-β, IGF-1 and PDGF, as suggested by Santos et al. and Wilson et al.

The Examiner also alleges that it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to make the composition of Hansson et al. in a 50:50 or 20:80 to 80:20 tripolyphosphate to water soluble chitosan weight % because Shu et al. teaches 4% chitosan and 1% tripolyphosphate.

Additionally, the Examiner alleges that it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to add βig-h3 at the concentration of 100 μg/ml ~ 1 mg/ml or 300 μg/ml ~ 600 μg/ml, as suggested by Kim et al., to the composition of Hansson et al.

2. 35 USC 103(a) Requirements

It is urged that the Examiner has not made a proper *prima facie* case of obviousness. Reconsideration and removal of the rejection is therefore proper and earnestly requested. The Examiner is reminded that there must be a motivation to combine and an expectation of success. A showing of obviousness requires a motivation or suggestion to combine or modify prior art references, coupled with a reasonable expectation of success. The motivation and the expectation of success must be found in the prior art references. *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.* 229 F.3d 1120, 56 USPQ2d 1456, (Fed. Cir. 2000) A *prima facie* case of obviousness is thus a showing by the Examiner that the motivation to combine the references and a reasonable expectation of success are found in the prior art references themselves. (Emphasis added).

3. Santos et al. Does Not Teach or Suggest Modifying the Composition of Hansson et al. to Provide the Claimed Invention.

The teachings of Hansson et al. were reviewed above in D1. Moreover, there is no suggestion to modify the composition as suggested by the Examiner.

Santos et al. relates to polymeric drug delivery systems, such as polymeric microspheres. Santos et al. teaches chitosan microspheres including chitosan and tripolyphosphate. Santos et al. also teaches that the microspheres can include FGF, PDGF, EGF and TGF-beta. Santos et al. does not, however, disclose the type of compositions required by Hansson et al. or that non-microsphere based systems should be used. Santos et al. does **not** teach or suggest that the Santos combination be modified or that βig-h3 be added to chitosan at a concentration of 100 μg/ml ~ 1 mg/ml. Furthermore, since Santos et al. relates to drug delivery systems, it would not have been obvious to provide βig-h3 in compositions for stimulating bone-formation and bone-consolidation. Thus, the Examiner has not established a *prima facie* case of obviousness by showing that the motivation to combine the two references and a reasonable expectation of success are found in the prior art references.

Even if those skilled in the art modify the composition of Hansson et al. as taught by Santos et al., it does not make the claimed invention obvious. The composition of Hansson et al. adapted as taught by Santos et al. would contain chitosan microspheres with tripolyphosphate. It would still not contain the βig-h3 at a concentration of 100 μg/ml ~ 1 mg/ml in the water-soluble

chitosan, nor the water-soluble chitosan and the tripolyphosphate in the mixed ratio of 20:80 ~ 80:20 weight %. Thus, the claimed invention is distinguishable over the composition of Hasson et al adapted as taught by Santos, et al.

As such, it is urged that the present invention is not obvious, and reconsideration and removal of the rejection is respectfully requested.

4. Wilson et al. Does Not Teach or Suggest Modifying the Composition of Hansson et al. to Provide the Claimed Invention.

Wilson et al. discloses dose-dependent responses of Xenupus ectodermal cells to morphogenic proteins. Wilson et al. teaches administering morphogenic proteins at concentrations from 1 ng/mg to 100 ng/mg to the ectodermal cells. Wilson et al. does **not** however teach or suggest adding βig-h3 to chitosan of a composition of Hansson et al. at a concentration of 100 μg/ml ~ 1 mg/ml to provide compositions for stimulating bone-formation and bone-consolidation. Additionally, pending claims as amended do not recite bone morphogenic protein. Thus, the shortcomings of Hansson et al. would not be overcome by the teachings of Wilson et al. It is therefore urged that the Examiner has not established a *prima facie* case of obviousness by showing that the motivation to combine the two references and a reasonable expectation of success are found in the prior art references.

Even if those skilled in the art modify the composition of Hansson et al. as taught by Wildson et al., it does not make the claimed invention obvious. The composition of Hansson et al. adapted as taught by Wilson et al. would not contain the βig-h3 in the water-soluble chitosan, nor the water-soluble chitosan and the tripolyphosphate in the mixed ratio of 20:80 ~ 80:20 weight %.

As such, it is urged that the present invention is not obvious, and reconsideration and removal of the rejection is respectfully requested.

5. Shu et al. Does Not Teach or Suggest Modifying the Composition of Hansson et al. to Provide the Claimed Invention.

Shu et al. relates to controlled drug delivery systems. Shu et al. discloses tripolyphosphate/chitosan complex beads for sustained drug release. In Shu et al., compositions

for the drug delivery systems include 4% chitosan and 1% tripolyphosphate.

Shu et al. does **not**, however, teach or suggest adding βig-h3 at a concentration of 100 μg/ml ~ 1 mg/ml to the chitosan. Furthermore, Shu et al. relates to sustained drug delivery systems, it would not have been obvious to have added βig-h3 to a composition of Hanssan et al. to provide compositions for stimulating bone-formation and bone-consolidation. Thus, Shu, et al. does not cure the deficiencies of Hansson et al. It is therefore urged that the Examiner has not established a *prima facie* case of obviousness by showing that the motivation to combine the two references and a reasonable expectation of success are found in the prior art references.

Even if those skilled in the art modify the composition of Hansson et al. as taught by Shu et al., it does not make the claimed invention obvious. The composition of Hansson et al. adapted as taught by Shu et al. would not contain the βig-h3 in the water-soluble chitosan at the required concentration.

As such, it is urged that the present invention is not obvious, and reconsideration and removal of the rejection is respectfully requested.

6. Kim et al. Does Not Teach or Suggest Modifying the Composition of Hansson et al. to Provide the Claimed Invention.

Kim et al. relates to βig-h3 roles in osteogenesis. Kim et al. teaches administering 50 μg/ml and 100 μg/ml of βig-h3 during osteoblast differentiation.

Contrary to what the Examiner contends, those of ordinary skill in the art would **not** be motivated to modify the composition of Hansson et al. by adding βig-h3 at a concentration of 100 μg/ml – 1 mg/ml to stimulate bone-formation and bone-consolidation. Kim et al. explicitly teaches that βig-h3 **inhibits** bone nodule formation. See paragraph entitled "Imobilized and Soluble Recombinant βig-h3 Proteins **Inhibited** Bone Nodule Formation of Osteoblasts" at page 174 of Kim et al. Moreover, Kim et al. is silent concerning adding βig-h3 to a chitosan solution along with tripolyphosphate.

More specifically, Kim et al. states that "Bone nodule formation was examined at day 21 in βig-h3 or FN-coated wells. As shown in Figure 5, βig-h3-coated wells showed progressively less Alizarin-positive bone nodules as the concentration of βig-h3 increased. **At 100 μg/ml** of βig-h3, **no** Aliazrin-stained bone nodules were observed". Additionally, Kim et al. teaches that "βig-h3-mediated inhibition of bone nodule formation was also observed when it was added as a

soluble form in a dose-dependent manner". Kim et al. further suggests that βig-h3 is involved in the early stage of bone formation and plays a **negative** role as a regulator of osteoblast differentiation. See at page 177, left column, lines 18-22.

With the reasons stated above, Kim et al. teaches away adding βig-h3 of as high as 100 μg/ml – 1 mg/ml to the composition of Hansson et al. In fact, Kim et al. supports the non-obviousness of the claimed invention.

Thus, the Examiner has not established a *prima facie* case of obviousness by showing that the motivation to combine the two references and a reasonable expectation of success are found in the prior art references.

Even if those skilled in the art modify the composition of Hansson et al. as taught by Kim et al., it does not make the claimed invention obvious. The composition of Hansson et al. adapted as taught by Kim et al. would not contain βig-h3 in the water-soluble chitosan at the required concentration of 100 μg/ml -1 mg/ml and the water-soluble chitosan and the tripolyphosphate in the required ratio of 20:80 ~ 80:20 weight %.

As such, it is urged that the present invention is not obvious, and reconsideration and removal of the rejection is respectfully requested.

F. FEES

This response is being filed with a petition for a one-month extension of time. A credit card authorization form to charge the required fee of $60.00 is attached. No further fee is believed to be due. If it is determined that any further fees are due or any overpayment has been made, the Assistant Commissioner is hereby authorized to debit or credit such sum to deposit account 02-2275. Pursuant to 37 C.F.R. 1.136(a)(3), please treat this and any concurrent or future reply in this application that requires a petition for an extension of time for its timely submission as incorporating a petition for extension of time for the appropriate length of time. The fee associated therewith is to be charged to Deposit Account No. 02-2275.

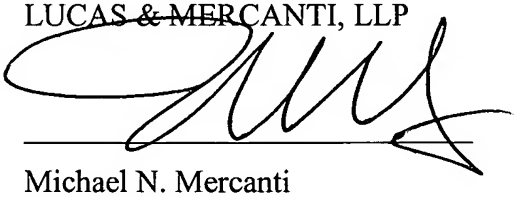
G. CONCLUSION

In view of the actions taken and remarks presented, it is respectfully submitted that each and every one of the matters raised by the Examiner has been addressed by the present amendment and that the present application is now in condition for allowance.

An early and favorable action on the merits is earnestly solicited.

Respectfully submitted,

LUCAS & MERCANTI, LLP



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